

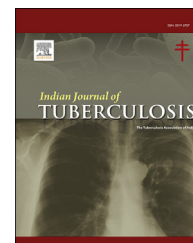


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Review article

Hydroxychloroquine and COVID-19 – A narrative review

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ABSTRACT

COVID 19 infection is unarguably the worst pandemic of this century. Till date there is no promising drug and vaccine available to treat this deadly viral infection. In the early phase chloroquine phosphate and hydroxychloroquine sulphate have been used to fight this illness on the basis of handful observational and small randomized and small-randomized studies. The paucity of clinical evidences of an unequivocal beneficial effect of chloroquine and hydroxychloroquine on COVID-19 has resulted in the passionate use of the drug for moderate to severe cases only and stimulated the need for large clinical trials for this and other molecules. In this review, we describe in brief the mechanism of action, the clinical studies, factors for cardiac toxicity, guidelines and future directions for hydroxy-chloroquine use in management of COVID-19 infection.

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1. Introduction

Novel Coronavirus disease 19 (COVID-19) infection has emerged as an pandemic which in a short window of four months has affected more than 4 million people around the world.¹ The index case of COVID-19 which was reported in the penultimate days of past year from Wuhan city, Hubei province, People's Republic of China, and thereafter has spread like wildfire across 190 countries.

Corona viruses (SARS-COVID) are crown shaped, positive sense single stranded RNA viruses belonging to Coronaviridae family. They are enveloped viruses. They most commonly inhabit in avian and mammalian species. The present iteration of the virus owes its origin from bats while the previous

versions had emerged from cats in 2002-04 and from camels in 2012 respectively.

With the myriad number of patients affected the virus has already taken a toll on the health system and resources across the globe. Not only hospitals have been overwhelmed with patients and the Intensive care units (ICU) filled up to the brim but also many frontline health workers including nurses and doctors succumbed to the illness. Hence there is imminent need to find a potential treatment for this deadly illness. At present there are various promising therapies being tried including Remdesivir, Lopinavir/ritonavir, Chloroquine (CQ) and Hydroxychloroquine (HCQS), Umifenovir (Arbidol), tocilizumab and plasma therapy.² In this review we describe in brief the pharmacology, the trials, regimens, adverse effects and guidelines related to hydroxychloroquine/chloroquine.

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Table 1 – Difference between properties of chloroquine and Hydroxychloroquine.

Properties	Chloroquine	Hydroxychloroquine
Structure	Amine acidotrophic form of quinine	Hydroxyl derivative of chloroquine
Water solubility	Less water soluble	More water soluble
Adverse effects	More toxic	40% less toxic than CQ
Effective concentration	Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC_{50}) four times higher than HCQS chloroquine: $EC_{50} = 23.90 \mu M$	Hydroxychloroquine has in vitro activity with a lower EC_{50} for SARS-CoV-2 compared with chloroquine after 24 hours of growth (hydroxychloroquine: $EC_{50} = 6.14 \mu M$)
Character	Weak base	Weak base
t _{1/2} Half life	Peak plasma levels occur 3–4 hours after each dose, with a terminal half-life of 40–50 days	Similar to CQ

[HCQS- hydroxychloroquine; CQ-chloroquine].

2. Chloroquine – a precursor to HCQS

Chloroquine (CQ) was first the drug to be evaluated for efficacy against SARS-CoV2 infection with severe acute respiratory syndrome. The antiviral, anti-inflammatory and immunomodulatory properties of CQ led to clinical testing of this drug as an experimental treatment in China and on the basis of initial success from small results it was advocated by the National Health Commission guidelines of the people's Republic of China.³ This document established the use of chloroquine nationwide for patients with COVID-19, at a recommended adult dose of 500 mg twice per day for a maximum of 10 days.

Chloroquine (CQ) is a widely utilized drug for prophylaxis and treatment of Malaria. Hydroxychloroquine (HCQS) is a hydroxyl derivative of chloroquine. It is more water soluble, less toxic and has fewer side effects than chloroquine (Table 1).⁴ CQ and HCQS are metabolized by cytochrome P450 in the liver, however 50% of the metabolites excreted by kidney without any modification. CQ has large volume of distribution and a tendency to accumulate in tissues at higher levels compared with plasma concentration. The elimination half-life of CQ is between 20 and 60 days.^{5–7} The toxic dose of CQ in adults is about 5 gram.⁵ Some prior studies had hinted at antiviral activities of the molecule with the drug hindering fusion of virus and glycosylation of its receptors.^{8,9}

In preclinical studies, chloroquine was found to have in vitro activity against COVID-19.¹⁰ Based on the data of 100 patients in over a dozen trials across 10 centers, where chloroquine resulted in radiological clearing and shortening the hospital course, the national health commission approved the use of at chloroquine.¹¹ Borba et al tested two doses of CQ in COVID-19- 600mg twice daily for 10 days and 450 mg twice daily for a day, once daily thereafter for 4 days.¹² There was no difference in lethality of disease amongst the two doses of CQ. Rather the high dose groups had more QT prolongation questioning the rationale use of high doses.

The Chinese health commission guideline initially recommended the dose of CQ 500 mg twice per day to the maximum course of 10 days but this regimen was more aggressive. Toxic effects of chloroquine were retinopathy and immunosuppression in early studies. The treatment guidelines were amended in late February, curtailing the maximum course duration to 7 days.¹³ They also recommended lower dose for

patients less than 50 kg and contraindicated the drug in pregnancy. Though chloroquine is recommended in China for the treatment of Covid-19, but high-quality data are lacking to show whether it or hydroxychloroquine is safe and effective for this indication. Recently, the US food and Drug Administration (USFDA) has issued a caution and restricted the use of CQ for the management COVID-19 outside of hospital or a clinical trial due to the risk of arrhythmia.¹⁴

3. HCQS – first among equals

HCQS is the less toxic derivative of chloroquine and has been utilized to treat COVID 19 as an alternative. The molecule was first synthesized by Hans Andersag in 1934 as an analogue of chloroquine (CQ) with higher water solubility.

In vitro studies have shown that HCQS can inhibit virus entry, transmission and replication.^{15,16} The mechanism of action include raising the PH of cellular endosomes to inhibit viral entry as well as replication and glycosylation of virus surface receptors ACE-2.¹⁷ Apart from antiviral activity, miscellaneous actions of HCQS include immune modulation, anti-inflammatory properties and regulation in pro inflammatory cytokines e.g. tumor necrosis factors (TNF), interleukin (IL)1 & 6 and antioxidant activities. In severe or critical illness cases of Covid-19, a cytokine storm exists and effects the prognosis of COVID-19 disease.¹⁸ The immunomodulatory effect of HCQS can be the additional avenue for mechanistic benefit. In fact, IL 6 antibody blocker-tocilizumab, interferon- λ and transfusion of convalescent plasma have been applied to counteract the cytokine storm.

HCQS is a cheap drug, easily available and seems to be safe too. The drug is not recommended for prophylaxis in children under 15 year of age.

4. Clinical data of HCQS in COVID

On the basis of different observational and some randomized trial (Table 2) HCQS has been recommended in different guidelines including some national policies.

Chen et al were the first to demonstrate efficacy of the drug in early March 2020. Empirical use of HCQS resulted in significantly less time for normalization of body temperature (2.2 ± 0.4 days) compared to the control group (3.2 ± 1.3 days),

lesser number of cough days were observed in the HCQS group (2.0 ± 0.2 days vs. 3.1 ± 1.5 day) and a significant decline in the radiological progression.¹⁹

The French collaborative studies led by **Gautret et al** subsequently demonstrated the efficacy HCQS in combination with azithromycin (Az) in attenuation of the viral load in patients with COVID 19.^{20,21} In the first prospective open level randomized control trial, hospitalized COVID 19 patients age >12 years were included. The principal exclusion criteria included prior allergy to HCQS, Retinopathy, G6PD deficiency and risk of QT prolongation. This study revealed that HCQS + Azithromycin (AZ) combination was potent in clearing viral load from nasopharyngeal site in only three to six days. A significant difference was observed between HCQS-treated patients and controls starting as early as day 3 post-inclusion. The second one was a pilot study in which 80 patients were enrolled and got 200 mg HCQS three times a day for 10 days and azithromycin 500 mg on day 1, 250 mg on days 2–5. The viral load decreased significantly with therapy. These three preliminary studies pitchforked hydroxychloroquine into the limelight for reduction pf duration of hospital stay and improve the prognosis of COVID-19-related pneumonia.

Jun et al more recent in a study from China in individuals with COVID- 19 found no difference in the rate of virologic clearance at 7 days with or without 5 days of hydroxychloroquine, and no difference in clinical outcomes (duration of hospitalization, temperature normalization, radiological progression).²²

Tang et al conducted a randomized open label study in 150 patients hospitalized for COVID-19.²³ The addition of HCQS to the standard of care did not result in a higher negative viral seroconversion. However, there was alleviation of clinical symptoms compared to standard care arm who were not receiving antiviral treatment. The possible mechanism of improvement was through anti-inflammatory effects. Adverse effect of high dose regimen (1200 mg/d) were seen in 30% but serious events were not different.

Million et al tested 1061 COVID-19 patients treated with HCQS + AZ combination for three days and eight days of follow-up the majority of patients had relatively mild disease at admission. Under these conditions, the treatment avoided worsening of the disease, as only 10 patients (0.9%) were transferred to the intensive care unit, but it also attenuated death rate, as only eight (0.75%) patients died. The drug also impaired persistent viral shedding.²⁴

Mahevas et al analyzed data of 181 patients hospitalized with COVID 19 pneumonia. In this study, 20.2% patients from HCQS group were transferred to the intensive care unit or died with in 7 days vs 22.1% in the non HCQS group. In the HCQS group 27.4% patients developed acute respiratory syndrome and 9.5% showed electrocardiogram changes which leads to discontinuation of drug.²⁵ Hence, the trial failed to demonstrate the usefulness of HCQS 600mg/d in COVID pneumonia.

Molina et al in their retrospective analysis of hospitalized COVID-19 patients, did not find any impact of HCQS use either with or without azithromycin, on the risk of mechanical ventilation. However, the use hydroxychloroquine as alone was associated with high mortality.²⁶

Joshua Gileris et al studied HCQS in 1376 patients, during a median follow-up of 22.5 days.²⁷ About 811 (58.9%) patients received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days); 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. Hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.

5. Pitfalls

The trials and studies were heterogenous in their inclusion criteria, drug dosing, duration and end points. Most of the studies had small sample size thus lacking sufficient power and leading to possible exaggeration of treatment effect. Many of the studies of COVID 19 tended not to include critically ill patients who could be receiving several other medications as well as having concomitant organ dysfunction like kidney and liver hepatic which both of which can alter the drug clearance from body leading to toxicity. Many studies have included virologic clearance and viral load as endpoints but the clinical significance of high viral load vis-à-vis cytokine storm in critically ill patients in seclusion is not yet known. Lack of a placebo arm and abundance of non-randomized studies is also of concern. Few of the studies discussed above are still in preprint (undergoing peer review; available from [medRxiv.org](https://www.medrxiv.org)) and yet to be published. The last and not the least, the issue of cardiovascular safety is discussed below.

6. HCQS and cardiovascular safety

Both HCQS and CQ have the tendency to mildly prolong QT interval on chronic use.²⁸ In critically ill patients, with renal and hepatic dysfunction these toxic effects would be more likely. This increase in QT prolongation serves as an indirect marker of risk of polymorphic ventricular tachycardia (VT) or torsade's de pointes with the drug. Since, such arrhythmia's can be life threatening drug induced QT prolongation becomes a pivotal parameter of safety. A caveat to be remember is that on a miniscule fraction of those with QT elongation will develop VT and arrhythmic mortality.²⁹ The QT interval corrected to the underlying heart rate is provides the most appropriate value and is termed as corrected QT interval (QTc). It can be calculated manually or the newer generation devices provide automated values.

Since both these drugs have the potential to prolong QT interval, a baseline electrocardiography (ECG) is essential prior to starting these drugs. Other precautions include frequent monitoring of hematological parameters (RBC, WBC and platelet counts), measurement of serum electrolytes, blood glucose (because of hypoglycemic potential of HCQS) and hepatic as well as renal functions. Co-administration of other drugs known to prolong the QTc interval must be avoided (**Fig. 1**). Azithromycin a drug used in the treatment COVID-19 also has the potential of QT prolongation.³⁰

In clinical studies with COVID -19, the rate of QT prolongation varies anywhere between 10% and 20% (**Table 3**).

Table 2 – Properties of different studies of Hydroxychloroquine (HCQS)/CQ in COVID -19.

Author	Study type	Treatment/Duration	Primary end point	Clinical outcomes
Chen et al ¹⁹ (2020)	Prospective open- label, non-randomized trial (n = 62)	Patients were assigned to receive HCQS (400 mg/d) treatment, for 5 days	Changes in time to clinical recovery (TTCR) of patients (fever, cough) Severe adverse reactions appeared was the observation endpoint	Significant response seen in temperature, cough and pneumonia in HCQS group
Gautret et al ²⁰ (2020)	Prospective open- label, non-randomized trial (n = 42) 26 patients received HCQS and 16 were control patients	HCQS(200 three times/day) alone (n = 14) for 10 days/ HCQS + Az(500 mg) on day 1, and 250 mg on days 2–5; (n = 6)	Viral load (nasopharyngeal swab): at day6; Virologic clearance over time, temperature, respiratory rate, and adverse effects	No significant difference in clinical status and duration of symptoms. HCQS treated patients were older than control patients (51.2 years vs. 37.3 years),
Gautret et al ²¹ (2020)	A pilot observational study (n = 80)	Hydroxychloroquine (200 mg every 8 h) for 10 days and azithromycin (500 mg on day 1, 250 mg on days 2–5)	Virologic clearance	Viral load decreased over time
Chorin et al, ³¹ 2020	Retrospective study (n = 84)	Patients were on HCQS + Azithromycin combination	Effect of HCQS/AZ on QT interval and risk for malignant arrhythmia	Development of ARF was a strong predictor of extreme QTc prolongation.
Million et al ²⁴ (2020)	Non-comparative observational study (n = 1061)	HCQS + Azithromycin for 3 days	Assess worsening and viral shedding persistence and death	Good clinical outcome and virologic cure were obtained in 973 patients within 10 days (91.7%).
Tang et al ²³ (2020)	Multi center open-label, randomized, controlled trial (N = 150)	200 mg daily for three days followed by a maintenance dose of 800 mg daily for the remaining days (total treatment duration:2 or 3 weeks for mild/moderate or severe patients, respectively).	28-day negative conversion rate of SARS-CoV-2.	The overall 28-day negative conversion rate was not different between SOC plus HCQS and SOC group (Kaplan–Meier estimates 85.4% versus 81.3%, P = 0.341
Jun et al ²² 2020	Pilot study (n = 30)	Hydroxychloroquine group (n = 15) HCQS 400 mg per day for 5 days plus conventional treatments. Control (n = 15). Conventional treatment alone..	Negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on days 7 after randomization	On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQS group and 14 (93.3%) cases in the control group
Molina et al ²⁶ 2020	Retrospective analysis, A total of 368 male patients were evaluated (HCQS, n = 97; HCQS + AZ, n = 113; no HCQS, n = 158)	Dosage and treatment length was not defined	Death, discharge and ventilator rate	Rates of death in the HC, HC + AZ, and no HC groups were 27.8%, 22.1%, 11.4%, respectively. Rates of ventilation in the HC, HCQS + AZ, and no HC groups were 13.3%, 6.9%, 14.1%, respectively.
Mahévas et al ²⁵ (2020)	Observational study(n = 181)	84 received HCQS 600mg/day in the first 48 hrs after hospitalization, 97 received no HCQS But delayed for at least 48 hr.	Transfer to intensive care unit (ICU) within 7 days from inclusion and/or death from any cause.	These results do not support the use of HCQS with positive hypoxic pneumonia.
Borba et al ¹² (2020)	Parallel, double-masked, randomized, Phase IIb clinical trial (N = 81)	High-dose CQ (n = 41) (ie, 600mgCQ twice daily for 10 days) or low-dosage (n = 40) CQ (i.e., 450 mg twice daily on day 1 and once daily for 4 days	Reduction in lethality by at least 50% in the high-dosage group compared with the low-dosage group.	Lethality until day 13 was 39.0% in the high-dosage group (16 of 41) and 15.0% in the low-dosage group (6 of 40).

[CQ- Chloroquine; HCQS- Hydroxychloroquine; AZ-Azithromycin; SOC- standard of care].

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Anti tubercular drugs	Miscellaneous
<ul style="list-style-type: none"> • Amiodarone • Sotalol • Quinidine • Procainamide • Ibutilide 	<ul style="list-style-type: none"> • Levofloxacin • Ciprofloxacin • Moxifloxacin • Clarithromycin • Azithromycin • Erythromycin • Ketoconazole • Fluconazole • Itraconazole 	<ul style="list-style-type: none"> • Amitriptyline • Desepamine • Imipramine • Fluoxetine 	<ul style="list-style-type: none"> • Haloperidol • Quetiapine • Zipracidone 	<ul style="list-style-type: none"> • Bedaquiline • Delamanid • Clofazimine 	<ul style="list-style-type: none"> • Chloroquine • HCQS • Cisapride • Ondansetron

Fig. 1 – Commonly used drugs causing QT interval prolongation on ECG.

Moreover, addition of azithromycin to HCQS increased the risk of QTc prolongation. This was precisely the case in the study by Chorin et al who found that 11% patient had QTc >500 with the combination while 30% had QTc increase >60 ms.³² Mecuro et al provided more precise comparison between

monotherapy & combination therapy.³² The combination therapy experienced greater median change in QTc (23ms vs. 5.5ms), greater proportion of patients with QTc >500 (21% vs.19%) & higher fraction of subjects with increase in QTc > 60ms(13% vs. 3%). In corollary, recent data emerging in

Table 3 – Incidence of Cardiac and Other adverse effects of Hydroxy-chloroquine use for COVID -19 in various studies.

Author	Drugs and duration	Cardiac adverse effects	Other adverse effects	Remark
Borba et al ¹² (n = 81)	High-dose CQ (i.e, 600mg twice daily for 10 days) or low-dosage CQ (i.e, 450 mg twice daily on day 1 and once daily for 4 days)	QTc interval prolongation greater than 500 milliseconds was seen in 11 of 73 patients (15.1%) Ventricular tachycardia Seen in 2 of 73 pt (2.7%)	1 Patient developed rhabdomyolysis, in 2 patients, myocarditis was suspected based on CKMB elevation since the first day of hospitalization, suggesting myocarditis related to SARS-CoV-2 itself.	Lethality was 39.0% (16 of 41 patients) in the high-dosage group and 15.0% (6 of 40) in the low-dosage group.
Chorin et al ³¹ (n = 84)	HCQS + AZ combination	Significant QTc prolongation in HCQS 11%.		Baseline QTc>460 ms did not predict QTc prolongation.
Tang et al ²³ (N = 150)	HCQS 1200 mg OD X 3 days followed by a maintained dose of 800 mg OD the remaining days; Total treatment duration: 2 or 3 weeks for mild/moderate or severe patients, respectively	Sinus bradycardia (1.4%), hypertension(1.4%), orthostatic hypotension (1.4%) hypertriglyceridemia (1.4%),	Serious adverse events disease progression and upper respiratory infections in 2.9%, most common non serious adverse events was diarrhea in 10%.Blurred vision(1.4%), coagulation dysfunction(1.4%), and kidney injury were other side effects.	Any adverse effects seen in 21 of 70 patients (30%) in HCQS group.
Jun et al ²² (n = 30)	HCQS 400 mg per day for 5 days		Four cases (26.7%) of the HCQS group & 3 cases(20%) of the control group had transient diarrhea and abnormal LFT.	
Mahévas et al ²⁵ (n=106)	HCQS at a daily dose of 600 mg in the first 48 hours after hospitalization	7 had a QTc prolongation of more than 60 ms (including 1 with QTc > 500 ms)	In the HCQS group, 2.8% of the patients died within 7 days vs 4.6% in the no-HCQS group due to ARDS	8 (9.5%) experienced ECG modifications requiring HCQS discontinuation at a median of 4 days
Mercuro et al ³² (n=90)	HCQS vs. HCQS + AZ	11% had QTc increase of >60 ms, 20% had QTc >500. The median rise in QTc was higher with combination therapy (23ms vs. 5.5 ms). The corresponding rates of QTc >60 ms were also higher with combination arm (3% vs. 13%) as was the rate of QTc >500 ms (19% vs. 21%).	Intractable nausea; premature ventricular complex; Right bundle branch block; Torsades de pointes; Hypoglycemia	Combination therapy had greater potential for QT prolongation and arrhythmia

[HCQS- Hydroxy-chloroquine; CQ- Chloroquine; AZ- Azithromycin; ms-millisecond; LFT-liver function test; QTc- Corrected QT interval].

Table 4 – Tisdale assessment Risk score for drug associated QTc Prolongation.

Risk Factors	Points
Age \geq 68 years	1
Female sex	1
Loop diuretic	1
Serum K ⁺ (potassium) \leq 3.5 mEq/L	2
Admission QTc \geq 450 ms	2
Acute MI (myocardial infarction)	2
\geq 2 QTc prolonging drugs	3
Sepsis	3
Heart Failure	3
One QTc prolonging drug	3
A Tisdale score of <6 predicts low risk, 7–10 medium risk, and >11 high risk of drug associated QT prolongation. [QTc- Corrected QT interval].	

the second week of May found higher in hospital mortality with combination therapy in the New York state which was the COVID epicenter of USA.³³ The USFDA too has issued a warning against HCQS use outside a hospital setting or clinical trial setting.¹³

Hence, it is also essential to perform ECG daily if QTc is 450–500 msec. Chloroquine and HCQS should not be used concurrently with lopinavir/ritonavir and Remdesivir for anticipated QTc prolongation. Table 3 lists the cardiovascular and other side effects observed in different studies.

Known hypersensitivity, retinopathy, porphyria, epilepsy, pre-existing maculopathy, pregnancy, G6PD deficiency, recent myocardial infarction and QTc >500 msec are the major contraindications to HCQS. Chloroquine however is not contraindicated in pregnancy. High HCQS doses >600 mg BID were

also predictive of prolongation of QTc intervals. Higher HCQS doses need close monitoring to ensure cardiac safety and are best avoided.

A variety factors are known to increase risk of drug induced ventricular arrhythmia like female sex, structural heart disease, electrolyte disturbances, congenital long QT syndromes, concomitant QT prolonging drugs and hepatic/renal failure.³⁴ A risk score has been derived and validated by Tisdale et al, for prediction of drug associated QT prolongation (Table 4).

7. Guideline recommendation

HCQS is currently an essential part of treatment regimen in almost all of the recommendation across the globe as depicted in (Table 5). However, it should not be used as stand alone therapy in the management of COVID-19, as there is paucity of unequivocal data on effectiveness. The dose and duration varies across the globe and one needs to follow local guidelines.

8. Yin and Yang of managing a pandemic

The novel corona virus has posed a unique challenge by spreading across all continents of globe (except Antarctica) in a span of 5 months affecting more than 4 million people. Simultaneously it has caused $>3,00,000$ casualties worldwide including frontline health workers. The rapid spread and the lack of an approved drug against the virus has fueled the search for identifying the potency of currently plethora of

Table 5 – Different guidelines and their recommendation for HCQS/CQ use in COVID 19 infection.^{35–41}

Guidelines	Recommendation
Revised Guidelines on Clinical Management of COVID – 19 ICMR	<ul style="list-style-type: none"> Hydroxychloroquine (Dose 400mg BD – for 1 day followed by 200mgBD for 4 days) In combination with Azithromycin (500 mg OD for 5 days) These drugs should be administered under close medical supervision, with monitoring for side effects including QTc interval. ICMR, has also recommended the use of hydroxychloroquine for prophylaxis in HCWs and close contacts (400 mg twice daily for day 1 followed by once weekly for 7 weeks in case of HCWs and for 3 weeks for close contacts).
NIH COVID-19 Treatment guideline	Insufficient clinical data to recommend for
Interim Guidance on Management Pending Empirical Evidence. From an American Thoracic Society-led International Task Force	using chloroquine or hydroxychloroquine for the treatment of COVID-19
Position Statement of the Indian Society of Critical Care Medicine	For hospitalized patients with COVID-19 who have evidence of pneumonia, we suggest hydroxychloroquine (or chloroquine) on a case-by-case basis.
Expert consensus from Department of Science and Technology and Health Commission of Guangdong province, China	Dose recommended for hydroxychloroquine is 400 mg twice daily on day 1 followed by 200 mg twice daily from day 2 to day 4.
Italian Society of Infectious and Tropical Diseases (Lombardy Section)	Chloroquine phosphate 500 mg BID for 10 days.
Surviving Sepsis Campaign, The Society of Critical Care Medicine and the European Society of Intensive Care Medicine	<p>Mild to moderate COVID-19: Lopinavir/ritonavir plus Chloroquine 500 mg _ 2/day or Hydroxychloroquine 200 mg per day for 10 days. Severe or critical COVID-19: Remdesivir plus Chloroquine 500 mg 2/day or Hydroxychloroquine 200 mg per day for 10e20 days.</p> <p>Insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19 at this point of time.</p>

antiviral drugs against COVID-19. Because of both antiviral and immunomodulatory effects, both CQ & HCQS were tested against COVID-19. Though small and non-randomized, initial few studies from February and March provided a hope among both clinicians and patients alike against the massive fear and despair generated by the pathogen globally. The drugs were approved by major health care associations and national societies in varying doses. The wait for larger randomized studies had to be rationalized against the rising fatalities and hospitalizations due to the virus. Another dilemma posed by the pandemic is choosing between offering immediate relief and generating data for medical research.¹²

More recent data has highlighted the cardiotoxicity and increased mortality caused by HCQS. Pending the discovery of an effective agent or vaccine we will have to continue the compassionate use of the drug for treatment of COVID-19. However, careful selection of patients at who are at low risk of QT prolongation, prescribing lower doses and avoiding concomitant drugs which also prolong QT are measures to the tilt the benefit risk ratio in favor of HCQS.

9. Future directions

The WHO has announced the phase III/IV **SOLIDARITY** clinical trial to find an effective treatment of COVID-19 in collaboration with 100 countries including India.⁴² Four investigational therapies are being tried – Remdesivir, Lopinavir/ritonavir, HCQS and interferon beta 1. Rigorous search for a potential cure is on. A [ClinicalTrials.gov](https://clinicaltrials.gov) search using keywords “COVID-19” or “SARS-CoV 2” & “treatment” on 18th May 2020 yielded 1095 results. Out of them 593 studies are actively recruiting patients for COVID-19.

10. Conclusion

COVID- 19 has emerged as a rapidly spreading and worst pandemic of the century till date. HCQS due to its antiviral and immunomodulatory properties has been tried for COVID-19 infections. Initial positive data from multiple small studies led to an enthusiasm and endorsement of the drug by various guidelines. More recent studies have questioned the role of the drug and highlighted the cardiotoxicity especially when combined with azithromycin. Additional research is underway and until emergence of more data the passionate use of HCQS should continue under proper surveillance.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Coronavirus Disease (COVID-19)- Situation Report 116 : World Health Organization; 2020. Available form: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>. Accessed May 15, 2020.
2. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *J Am Med Assoc*. 2020. <https://doi.org/10.1001/jama.2020.6019>. available online April 13, 2020.
3. National Health Commission of the People's Republic of China. Interpretation of COVID-19 Treatment Guidelines (6th Version); Feb 19, 2020 (accessed April 2020, 2020; in Chinese) http://www.gov.cn/zhengce/2020-02/19/content_5480958.htm.
4. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. *Int J Antimicrob Agents*. 2020:105945.
5. Riou B, Barriot P, Rimailho A, Baud FJ. Treatment of severe chloroquine poisoning. *N Engl J Med*. 1988;318:1–6.
6. Tanenbaum L. Antimalarial agents. *Arch Dermatol*. 1980;116:587.
7. Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine. *Clin Pharmacokinet*. 1996;31:257–274.
8. Yan Y, Zou Z, Sun Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. *Cell Res*. 2013;23:300–302.
9. Li C, Zhu X, Ji X, et al. Chloroquine, a FDA-approved drug, prevents Zika virus infection and its associated congenital microcephaly in mice. *Biomedicine*. 2017;24:189–194.
10. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;11:267–271.
11. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14:72–73.
12. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4.23), e208857. <https://doi.org/10.1001/jamanetworkopen.2020.8857>.
13. National Health Commission of the People's Republic of China. Regarding Dosage Adjustments to the Experimental Use of Chloroquine Phosphate in the Treatment of COVID-19; Feb 26, 2020 [in Chinese] <http://www.nhc.gov.cn/xcs/zhengcwj/202002/0293d017621941f6b2a4890035243730.shtml>. Accessed February 29, 2020.
14. Hydroxychloroquine or Chloroquine for COVID-19: Drug Safety Communication - FDA Cautions against Use outside of the Hospital Setting or a Clinical Trial Due to Risk of Heart Rhythm Problems. Drug Safety Communication-FDA.24.04.2020.[Internet] Available form: <https://www.fda.gov/safety/medical-product-safety-information/hydroxychloroquine-or-chloroquine-covid-19-drug-safety-communication-fda-cautions-against-use>. Accessed: May 15, 2020
15. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020. <https://doi.org/10.1093/cid/ciaa237>. published online March 9.
16. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16.
17. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol*. 2020;16:155–166.

18. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect.* 2020;80(6):607–613.
19. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *Med Rxiv Prepr Serv Health Sci.* 2020. <https://doi.org/10.1101/2020.03.22.20040758>.
20. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* 2020. <https://doi.org/10.1016/j.ijantimicag.2020.105949>. published online March 20.
21. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. *Trav Med Infect Dis.* 2020;34:101663. <https://doi.org/10.1016/j.tmaid.2020.101663>.
22. Jun C, Danping L, Chen Jun LD, Liu Ping, Xu Qingnian, Xia Lu. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ Med Sci.* 2020;49(1), 2020 0-0.
23. Tang W, Cao Z, Han M, et al. Hydroxy-chloroquine in patients with COVID-19: an open-label, randomized, controlled trial. *medRxiv.* 2020. <https://doi.org/10.1101/2020.04.10.20060558>.
24. Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, Amrane S. Early Treatment of COVID-19 Patients with Hydroxychloroquine and Azithromycin: A Retrospective Analysis of 1061 Cases in Marseille, France. *Travel Med Infect Dis;* 2020:101738. <https://doi.org/10.1016/j.tmaid.2020.101738> [published online ahead of print, 2020 May 5].
25. Mahevas M, Tran VT, Roumier M, et al. Clinical Efficacy of Hydroxychloroquine in Patients Hospitalized for COVID 19 Infection with Oxygen Requirement: observational comparative study using routine care data. *BMJ.* 2020:369. m1844.
26. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Maladies Infect.* 2020;50:384.
27. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* 2020. <https://doi.org/10.1056/NEJMoa2012410>. Available online on May 7th 2020.
28. Morgan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. *J Clin Rheumatol.* 2013;19(5):286–288.
29. Simpson T, Salazar J, Vittinghoff E, et al. Association of QT prolonging medications with risk of autopsy causes of sudden death. *JAMA Int Med.* 2020;180(5):1–9.
30. Mosholder AD, Mathew J, Alexander JJ, Smith H, Nambiar S. Cardiovascular risks with azithromycin and other antibacterial drugs. *N Engl J Med.* 2013;368(18):1665–1668.
31. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nat Med.* 2020. <https://doi.org/10.1038/s41591-020-0888-2> [available online on 24th April 2020].
32. Mercurio NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for COVID-19. *JAMA Cardiol.* 2020. <https://doi.org/10.1001/jamacardio.2020.1834>. Available online on 1st May 2020.
33. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *J Am Med Assoc.* 2020. <https://doi.org/10.1001/jama.2020.8630> [Published online on May 11,2020].
34. Tisdale JE, Jayes HA, Kingery JR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes.* 2013;6:479–487.
35. Indian Council for Medical Research. Recommendation for Empiric Use of Hydroxychloroquine for Prophylaxis of SARS-CoV-2 Infection. Available from: https://icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM_V2.pdf. [accessed 30 April 2020].
36. COVID 19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID 19) Treatment Guidelines. National Institute Of Health Available at: <https://www.covid19treatment.guidelines.nih.gov/> [Accessed 19/5/2020].
37. Wilson KC, Chotirmall SH, Bai C, Rello J. COVID-19: Interim Guidance on Management Pending Empirical Evidence. Last updated April 3, 2020. Available at: www.thoracic.org/professionals/clinical-resources/disease-related-resources/covid-19-guidance.pdf.
38. Javeri Y, Jagathkar G, Dixit S, et al. Indian society of critical care medicine position statement for central venous catheterization and management 2020. *Indian J Crit Care Med.* 2020 Jan;24(suppl 1):S6–S30.
39. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jiehe He Huxi Zazhi.* 2020 Mar 12;43(3):185e8. <https://doi.org/10.3760/cma.j.issn.1001-0939.2020.03.009>.
40. <http://www.simit.org/medias/1555-covid19-linee-guida-trattamento-01mar.pdf>. Last accessed on 19 April 2020.
41. Alhazzani W, Möller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med.* 2020;46(5):854–887.
42. Solidarity Clinical Trial for COVID-19 treatments. World Health Organization. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>. [Accessed: May 15, 2020].